CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 074220

Trade Name : CORMAX 0.05% CREAM

Generic Name: Clobetasol Propionate Cream USP 0.05%

Sponsor : Healthpoint, Ltd.

Approval Date: May 16, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 074220

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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 074220

APPROVAL LETTER

DJV

ANDA 74-220

MAY 16 1997

HEALTHPOINT, LTD.
Attention: Richard Hamer Associates, Inc.
Agent for Healthpoint, Ltd.
100 East 15th Street, Suite 320
Ft. Worth, TX 76102-0598

Dear Sir:

This refers to your abbreviated new drug application dated June 22, 1992, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Cormax™ (Clobetasol Propionate Cream, USP) 0.05%.

Reference is also made to your amendments dated November 11, 1994, July 7, 1995, April 15, December 18 and 23, 1996, and March 27, April 4 and 11, 1997.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined that your Clobetasol Propionate Cream USP, 0.05% is bioequivalent and, therefore therapeutically equivalent, to the listed drug (Temovate® Cream 0.05% of Glaxo Wellcome Inc.).

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FDA-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FDA-2253 at the time of their initial use.

Sincerely yours,

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074220

FINAL PRINTED LABELING

Cormax™ 0.05% Cream
(Clobetasol Propionate Cream, USP)
60 g Tube

Oclassen
PHARMACEUTICALS, INC

Cormax™ 0.05% Cream
(Clobetasol Propionate Cream, USP)

60 g

NDC 55515-420-60

N 3 55515-420-45 5

Caution: Federal (U.S.A.) law prohibits dispensing without prescription.

LOT/EXP

FOR DERMATOLOGIC USE ONLY - NOT FOR OPHTHALMIC USE

Important: The opening of this product is covered by a tamper-resistant seal. If this seal has been punctured or is not visible do not use and return product to place of purchase.

To Open: To puncture the seal, reverse the cap and place the puncture-top onto the tube. Push down firmly until seal is open. To close, screw the cap back onto the tube.

Store at controlled room temperature 15° to 30°C (59° to 86°F). Do not refrigerate.

Mfd. for Oclassen PHARMACEUTICALS, INC. San Antonio, TX 78215
Packaged by DPT Laboratories, Inc. San Antonio, TX 78215

110666-0496

Each gram contains: 0.5 mg clobetasol propionate in a cream base composed of white petrolatum, cetyl alcohol, stearyl alcohol, lanolin oil, PEG-8 stearate, polysorbate 60, glycol stearate, propylparaben, propylene glycol, methylparaben and purified water.

Usual Dosage: See package insert for complete prescribing information.

60 g

NDC 55515-420-60

Cormax™ 0.05% Cream

(Clobetasol Propionate Cream, USP)

Oclassen PHARMACEUTICALS, INC.

Caution: Federal (U.S.A.) law prohibits dispensing without prescription.

FOR DERMATOLOGIC USE ONLY - NOT FOR OPHTHALMIC USE.

USUAL DOSAGE: See package insert for complete prescribing information.

Each gram contains: 0.5 mg clobetasol propionate in a cream base composed of white petrolatum, cetyl alcohol, stearyl alcohol, lanolin oil, PEG-8 stearate, polysorbate 60, glycol stearate, propylparaben, propylene glycol, methylparaben and purified water.

Store at controlled room temperature 15° to 30°C (59° to 86°F).

Do not refrigerate.

IMPORTANT: Do not use if seal has been punctured or is not visible.

TO OPEN: Use cap to puncture seal.

See crimp for lot no. and expiration date.

Mfd. for Oclassen Pharmaceuticals, Inc., San Rafael, CA 94901,
by DPT Laboratories, Inc., San Antonio, TX 78215

103790-0496

Cormax
0.05% Cream
(Clobetasol Propionate Cream,USP)

45 g Tube

Oclassen
PHARMACEUTICALS, INC.

45 g

Cormax™ 0.05% Cream
(Clobetasol Propionate Cream, USP)

NDC 55515-420-45

N 3 55515-420-45 5

Caution: Federal (U.S.A.) law prohibits dispensing without prescription.

LOT/EXP

Each gram contains: 0.5 mg clobetasol propionate in a cream base composed of white petrolatum, cetyl alcohol, stearyl alcohol, lanolin oil, PEG-8 stearate, polysorbate 60, glycol stearate, propylparaben, propylene glycol, methylparaben and purified water.

Usual Dosage: See package insert for complete prescribing information.

FOR DERMATOLOGIC USE ONLY - NOT FOR OPHTHALMIC USE

Important: The opening of this product is covered by a tamper-resistant seal. If this seal has been punctured or is not visible do not use and return product to place of purchase.

To Open: To puncture the seal, reverse the cap and place the puncture-top onto the tube. Push down firmly until seal is open. To close, screw the cap back onto the tube.

Store at controlled room temperature 15° to 30°C (59° to 86°F). Do not refrigerate.

Mfd. for
Oclassen
PHARMACEUTICALS, INC.
San Rafael, CA 94901
by DPT Laboratories, Inc.
San Antonio, TX 78215

110655-0498

45 g

NDC 55515-420-45

Cormax™ 0.05% Cream

(Clobetasol Propionate Cream, USP)

Oclassen
PHARMACEUTICALS, INC.

Caution: Federal (U.S.A.) law prohibits dispensing without prescription.

FOR DERMATOLOGIC USE ONLY - NOT FOR OPHTHALMIC USE.

USUAL DOSAGE: See package insert for complete prescribing information.

Each gram contains: 0.5 mg clobetasol propionate in a cream base composed of white petrolatum, cetyl alcohol, stearyl alcohol, lanolin oil, PEG-8 stearate, polysorbate 60, glycol stearate, propylparaben, propylene glycol, methylparaben and purified water.

Store at controlled room temperature 15° to 30°C (59° to 86°F). Do not refrigerate.

IMPORTANT: Do not use if seal has been punctured or is not visible.

TO OPEN: Use cap to puncture seal. See crimp for lot no. and expiration date.

Mfd. for Oclassen Pharmaceuticals, Inc., San Rafael, CA 94901
by DPT Laboratories, Inc., San Antonio, TX 78215

103794-0696

Each gram contains: 0.5 mg clobetasol propionate in a cream base composed of white petrolatum, cetyl alcohol, stearyl alcohol, lanolin oil, PEG-8 stearate, polysorbate 60, glycol stearate, propylparaben, propylene glycol, methylparaben and purified water.

Usual Dosage: See package insert for complete prescribing information.

LOT/EXP

Oclassen PHARMACEUTICALS, INC

Cormax™ 0.05% Cream
(Clobetasol Propionate Cream, USP)

Caution: Federal (U.S.A.) law prohibits dispensing without prescription.

30 g

N 3 55515-420-30 1

NDC 55515-410-30

Cormax™ 0.05% Cream
(Clobetasol Propionate Cream, USP)
30 g Tube

FOR DERMATOLOGIC USE ONLY - NOT FOR OPHTHALMIC USE

Important: The opening of this product is covered by a tamper-resistant seal. If this seal has been punctured or is not visible do not use and return product to place of purchase.

To Open: To puncture the seal, reverse the cap and place the puncture-top onto the tube. Push down firmly until seal is open. To close, screw the cap back onto the tube.

Store at controlled room temperature 15° to 30°C (59° to 86°F). Do not refrigerate.

Mfd for Oclassen PHARMACEUTICALS, INC San Rafael, CA 94901 by PTI Laboratories, Inc. San Antonio, TX 78215

110654-0396

30 g

NDC 55515-420-30

Cormax™ 0.05% Cream

(Clobetasol Propionate Cream, USP)

Oclassen
PHARMACEUTICALS, INC.

Caution: Federal (U.S.A.) law prohibits dispensing without prescription.

FOR DERMATOLOGIC USE ONLY - NOT FOR OPHTHALMIC USE.

USUAL DOSAGE: See package insert for complete prescribing information.

Each gram contains: 0.5 mg clobetasol propionate in a cream base composed of white petrolatum, cetyl alcohol, stearyl alcohol, lanolin oil, PEG-6 stearate, polysorbate 60, glycol stearate, propylparaben, propylene glycol, methylparaben and purified water.

Store at controlled room temperature 15° to 30°C (59° to 86°F). Do not refrigerate.
See crimp for lot no. and expiration date.

IMPORTANT: Do not use if seal has been punctured or is not visible.

TO OPEN: Use cap to puncture seal.

Mfd. for Oclassen Pharmaceuticals, Inc., San Rafael, CA 94901
by DPT Laboratories, Inc., San Antonio, TX 78215

103793-0696

Each gram contains: 0.5 mg clobetasol propionate in a cream base composed of white petrolatum, cetyl alcohol, stearyl alcohol, lanolin oil, PEG-8 stearate, polysorbate 60, glycol stearate, propylparaben, propylene glycol, methylparaben and purified water.

Usual Dosage: See package insert for complete prescribing information.

LOT/EXP

Oclassen
PHARMACEUTICALS, INC

Cormax™ 0.05% Cream
(Clobetasol Propionate Cream, USP)

Caution: Federal (U.S.A.) law prohibits dispensing without prescription.

15 g

NDC 55515-420-15

Cormax™ 0.05% Cream
(Clobetasol Propionate Cream, USP)
15 g Tube

FOR DERMATOLOGIC USE ONLY - NOT FOR OPHTHALMIC USE

Important: The opening of this product is covered by a tamper-resistant seal. If this seal has been punctured or is not visible do not use and return product to place of purchase.

To Open: To puncture the seal, reverse the cap and place the puncture-top onto the tube. Push down firmly until seal is open. To close, screw the cap back onto the tube.

Store at controlled room temperature 15° to 30°C (59° to 86°F). Do not refrigerate.

110653-0496

Mfd. for
Oclassen
PHARMACEUTICALS, INC
San Rafael, CA 94901
by DPT Laboratories, Inc
San Antonio, TX 78215

15 g

NDC 55515-420-15

Cormax™ 0.05% Cream

(Clobetasol Propionate Cream, USP)

Oclassen
PHARMACEUTICALS, INC.

Caution: Federal (U.S.A.) law prohibits dispensing without prescription.

FOR DERMATOLOGIC USE ONLY - NOT FOR OPHTHALMIC USE.

USUAL DOSAGE: See package insert for complete prescribing information.

Each gram contains: 0.5 mg clobetasol propionate in a cream base composed of white petrolatum, cetyl alcohol, stearyl alcohol, lanolin oil, PEG-8 stearate, polysorbate 60, glycol stearate, propylparaben, propylene glycol, methylparaben and purified water.

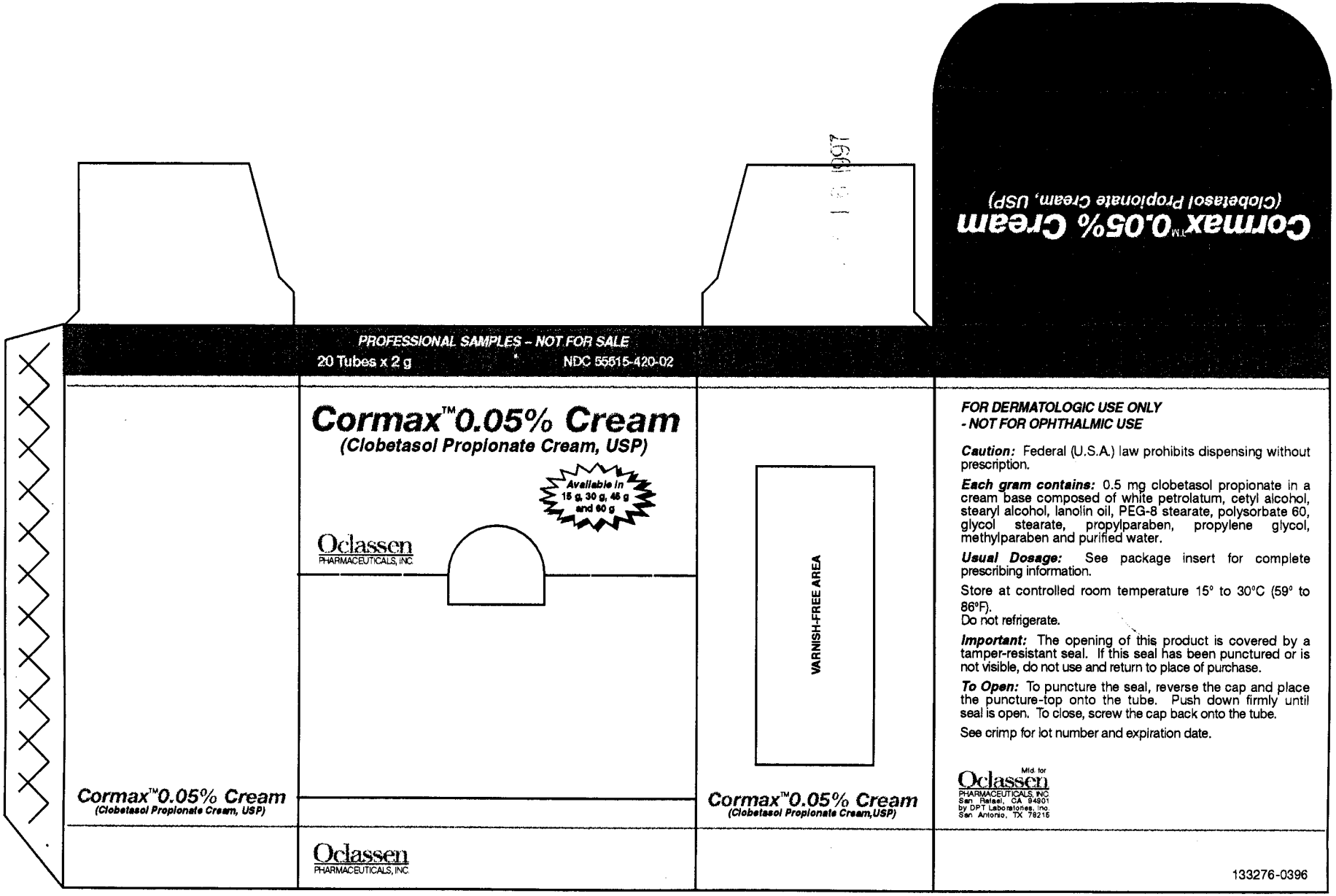
Store at controlled room temperature 15° to 30°C (59° to 86°F).

Do not refrigerate. See crimp for lot no. and expiration date.

IMPORTANT: Do not use if seal has been punctured or is not visible.

TO OPEN: Use cap to puncture seal.

Mfd. for Oclassen Pharmaceuticals, Inc., San Rafael, CA 94901
by DPT Laboratories, Inc., San Antonio, TX 78215 103792-0896


Cormax™0.05% Cream
(Clobetasol Propionate Cream, USP)
PROFESSIONAL SAMPLES – NOT FOR SALE
20 Tubes x 2 g
NDC 55515-420-02
Cormax™0.05% Cream
(Clobetasol Propionate Cream, USP)
Available in 15 g, 30 g, 45 g and 60 g
Oclassen PHARMACEUTICALS, INC
VARNISH-FREE AREA
Cormax™0.05% Cream
(Clobetasol Propionate Cream,USP)
FOR DERMATOLOGIC USE ONLY
- NOT FOR OPHTHALMIC USE
Caution: Federal (U.S.A.) law prohibits dispensing without prescription.
Each gram contains: 0.5 mg clobetasol propionate in a cream base composed of white petrolatum, cetyl alcohol, stearyl alcohol, lanolin oil, PEG-8 stearate, polysorbate 60, glycol stearate, propylparaben, propylene glycol, methylparaben and purified water.
Usual Dosage: See package insert for complete prescribing information.
Store at controlled room temperature 15° to 30°C (59° to 86°F).
Do not refrigerate.
Important: The opening of this product is covered by a tamper-resistant seal. If this seal has been punctured or is not visible, do not use and return to place of purchase.
To Open: To puncture the seal, reverse the cap and place the puncture-top onto the tube. Push down firmly until seal is open. To close, screw the cap back onto the tube.
See crimp for lot number and expiration date.
Mfd. for
Oclassen PHARMACEUTICALS, INC
San Rafael, CA 94901
by DPT Laboratories, Inc.
San Antonio, TX 78215
133276-0396

MAY 1 6 1997

PROFESSIONAL SAMPLE - NOT FOR SALE

2 g **NDC 99915-420-92**

Cormax™ Cream 0.05%

(Clobetasol Propionate Cream, USP)

Oclassen
PHARMACEUTICALS INC

Caution: Federal (U.S.A.) law prohibits dispensing without prescription

FOR EXTERNAL USE ONLY.
NOT FOR EYE USE.
USUAL DOSAGE: See package insert.
Store at 59° to 86°F.
Do not refrigerate.
Distributed by
Oclassen Pharmaceuticals, Inc.,
San Rafael, CA 94901

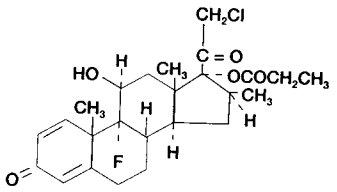
103778-0496

Cormax™ 0.05% Cream
(Clobetasol Propionate Cream, USP)

For Dermatologic Use Only - Not for Ophthalmic Use.

DESCRIPTION: Cormax™ (Clobetasol Propionate Cream, USP) contains the active compound clobetasol propionate, a synthetic corticosteroid, for topical dermatologic use. Clobetasol, an analog of prednisolone, has a high degree of glucocorticoid activity and a slight degree of mineralocorticoid activity.

Chemically, clobetasol propionate is 21-chloro-9-fluoro-11β,17-dihydroxy-16β-methylpregna-1,4-diene-3,20-dione 17-propionate and it has the following structural formula:



Clobetasol propionate has the molecular formula $C_{25}H_{32}ClFO_5$ and a molecular weight of 466.98. It is a white to cream-colored crystalline powder insoluble in water.

Each gram of Cormax™ (Clobetasol Propionate Cream, USP) contains 0.5 mg clobetasol propionate in a base composed of white petrolatum, cetyl alcohol, stearyl alcohol, lanolin oil, PEG-8 stearate, polysorbate 60, glycol stearate, propylparaben, propylene glycol, methylparaben and purified water.

CLINICAL PHARMACOLOGY: Like other topical corticosteroids, clobetasol propionate has anti-inflammatory, antipruritic, and vasoconstrictive properties. The mechanism of the anti-inflammatory activity of the topical steroids, in general, is unclear. However, corticosteroids are thought to act by the induction of phospholipase A_2 inhibitory proteins, collectively called lipocortins. It is postulated that these proteins control the biosynthesis of potent mediators of inflammation such as prostaglandins and leukotrienes by inhibiting the release of their common precursor, arachidonic acid. Arachidonic acid is released from membrane phospholipids by phospholipase A_2.

Pharmacokinetics: The extent of percutaneous absorption of topical corticosteroids is determined by many factors, including the vehicle and the integrity of the epidermal barrier. Occlusive dressing with hydrocortisone for up to 24 hours has not been demonstrated to increase penetration; however, occlusion of hydrocortisone for 96 hours markedly enhances penetration. Topical corticosteroids can be absorbed from normal intact skin. Inflammation and/or other disease processes in the skin may increase percutaneous absorption.

Studies performed with clobetasol propionate cream indicate that it is in the super-high range of potency as compared with other topical corticosteroids.

INDICATIONS AND USAGE: Cormax™ (Clobetasol Propionate Cream, USP) is a super-high potency corticosteroid formulation indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses. Treatment beyond 2 consecutive weeks is not recommended, and the total dosage should not exceed 50 g per week because of the potential for the drug to suppress the hypothalamic-pituitary-adrenal (HPA) axis. Use in children under 12 years of age is not recommended.

As with other highly active corticosteroids, therapy should be discontinued when control has been achieved. If no improvement is seen within 2 weeks, reassessment of the diagnosis may be necessary.

CONTRAINDICATIONS: Cormax™ (Clobetasol Propionate Cream, USP) is contraindicated in those patients with a history of hypersensitivity to any of the components of this preparation.

PRECAUTIONS:

General: Cormax™ (Clobetasol Propionate Cream, USP) should not be used in the treatment of rosacea or perioral dermatitis, and should not be used on the face, groin or axillae.

Systemic absorption of topical corticosteroids can produce reversible HPA axis suppression with the potential for glucocorticosteroid insufficiency after withdrawal from treatment. Manifestations of Cushing's syndrome, hyperglycemia, and glucosuria can also be produced in some patients by systemic absorption of topical corticosteroids while on therapy.

Patients applying a topical corticosteroid to a large surface area or to areas under occlusion should be evaluated periodically for evidence of HPA axis suppression. This may be done by using the ACTH stimulation, A.M. plasma cortisol, and urinary free cortisol tests. Patients receiving super-potent corticosteroids should not be treated for more than 2 weeks at a time, and only small areas should be treated at any one time due to the increased risk of HPA axis suppression.

Clobetasol propionate cream produced HPA axis suppression when used at doses as low as 2 g per day for 1 week in patients with eczema.

If HPA axis suppression is noted, an attempt should be made to withdraw the drug, to reduce the frequency of application, or to substitute a less potent corticosteroid. Recovery of HPA axis function is generally prompt upon discontinuation of topical corticosteroids. Infrequently, signs and symptoms of glucocorticosteroid insufficiency may occur, requiring supplemental systemic corticosteroids. For information on systemic supplementation, see prescribing information for those products.

Pediatric patients may be more susceptible to systemic toxicity from equivalent doses due to their larger skin surface to body mass ratios (see PRECAUTIONS: Pediatric Use).

If irritation develops, Cormax™ (Clobetasol Propionate Cream, USP) should be discontinued and appropriate therapy instituted. Allergic contact dermatitis with corticosteroids is usually diagnosed by observing *failure to heal* rather than noting a clinical exacerbation as with most topical products not containing corticosteroids. Such an observation should be corroborated with appropriate diagnostic patch testing.

If concomitant skin infections are present or develop, an appropriate antifungal

or antibacterial agent should be used. If a favorable response does not occur promptly, use of Cormax™ should be discontinued until the infection has been adequately controlled.

Information for Patients: Patients using topical corticosteroids should receive the following information and instructions:

1. This medication is to be used as directed by the physician. It is for external use only. Avoid contact with the eyes.
2. This medication should not be used for any disorder other than that for which it was prescribed.
3. The treated skin area should not be bandaged, otherwise covered or wrapped, so as to be occlusive unless directed by the physician.
4. Patients should report any signs of local adverse reactions to the physician.

Laboratory Tests: The following tests may be helpful in evaluating HPA axis suppression:

ACTH stimulation test
A.M. plasma cortisol test
Urinary free cortisol test

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term animal studies have not been performed to evaluate the carcinogenic potential of clobetasol propionate.

Studies in the rat following oral administration at dosage levels up to 50 mg/kg per day revealed that the females exhibited an increase in the number of resorbed embryos and a decrease in the number of living fetuses at the highest dose.

Clobetasol propionate was non-mutagenic in three different test systems: the Ames test, the *Saccharomyces cerevisiae* gene conversion assay, and the *E. coli* B WP2 fluctuation test.

Pregnancy: Teratogenic Effects: Pregnancy Category C: Corticosteroids have been shown to be teratogenic in laboratory animals when administered systemically at relatively low dosage levels. Some corticosteroids have been shown to be teratogenic after dermal application to laboratory animals.

Clobetasol propionate has not been tested for teratogenicity when applied topically; however, it is absorbed percutaneously, and when administered subcutaneously it was a significant teratogen in both the rabbit and mouse. Clobetasol propionate has greater teratogenic potential than steroids that are less potent.

Teratogenicity studies in mice using the subcutaneous route resulted in fetotoxicity at the highest dose tested (1 mg/kg) and teratogenicity at all dose levels tested down to 0.03 mg/kg. These doses are approximately 0.33 and 0.01 times, respectively, the human topical dose of Cormax™ (Clobetasol Propionate Cream, USP). Abnormalities seen included cleft palate and skeletal abnormalities. In rabbits, clobetasol propionate was teratogenic at doses of 3 and 10 mcg/kg. These doses are approximately 0.001 and 0.003 times, respectively, the human topical dose of Cormax™. Abnormalities seen included cleft palate, cranioschisis, and other skeletal abnormalities.

There are no adequate and well-controlled studies of the teratogenic potential of clobetasol propionate in pregnant women. Cormax™ should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in human milk. Because many drugs are excreted in human milk, caution should be exercised when Cormax™ (Clobetasol Propionate Cream, USP) is administered to a nursing woman.

Pediatric Use: Safety and effectiveness of Cormax™ (Clobetasol Propionate Cream, USP) in pediatric patients have not been established. Use in children under 12 years of age is not recommended. Because of a higher ratio of skin surface area to body mass, pediatric patients are at a greater risk than adults of HPA axis suppression and Cushing's syndrome when they are treated with topical corticosteroids. They are therefore also at greater risk of adrenal insufficiency during or after withdrawal of treatment. Adverse effects including striae have been reported with inappropriate use of topical corticosteroids in infants and children.

HPA axis suppression, Cushing's syndrome, linear growth retardation, delayed weight gain and intracranial hypertension have been reported in children receiving topical corticosteroids. Manifestation of adrenal suppression in children include low plasma cortisol levels, and an absence of response to ACTH stimulation. Manifestations of intracranial hypertension include bulging fontanelles, headaches, and bilateral papilledema.

ADVERSE REACTIONS: In controlled clinical trials, the most frequent adverse reactions reported for clobetasol propionate cream were burning and stinging sensation in 1% of treated patients. Less frequent adverse reactions were itching, skin atrophy, and cracking and fissuring of the skin.

Cushing's syndrome has been reported in infants and adults as a result of prolonged use of topical clobetasol propionate formulations.

The following additional local adverse reactions have been reported with topical corticosteroids, and they may occur more frequently with the use of occlusive dressings and higher potency corticosteroids. These reactions are listed in an approximately decreasing order of occurrence: dryness, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, secondary infection, irritation, striae, and miliaria.

OVERDOSAGE: Topically applied Cormax™ (Clobetasol Propionate Cream, USP) can be absorbed in sufficient amounts to produce systemic effects (see PRECAUTIONS).

DOSAGE AND ADMINISTRATION: Apply a thin layer of Cormax™ (Clobetasol Propionate Cream, USP) to the affected skin areas twice daily and rub in gently and completely.

Cormax™ is a super-high potency topical corticosteroid; therefore, **treatment should be limited to 2 consecutive weeks, and amounts greater than 50 g per week should not be used.**

As with other highly active corticosteroids, therapy should be discontinued when control has been achieved. If no improvement is seen within 2 weeks, reassessment of diagnosis may be necessary.

Cormax™ should not be used with occlusive dressings.

HOW SUPPLIED: Cormax™ (Clobetasol Propionate Cream, USP) 0.05% is supplied in 15 g (NDC 55515-420-15), 30 g (NDC 55515-420-30), 45 g (NDC 55515-420-45) and 60 g (NDC 55515-420-60) tubes.

Store at controlled room temperature 15° - 30° C (59° - 86° F). Do not refrigerate.

Caution: Federal law prohibits dispensing without prescription.

Mfd. for
Oclassen
PHARMACEUTICALS, INC.
San Rafael, CA 94901
by DPT Laboratories, Inc.
San Antonio, TX 78215

Revised: January, 1997.
127022-0197

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074220

CHEMISTRY REVIEW(S)

D W

1. CHEMISTRY REVIEW NO. 6

2. ANDA # 74-220

3. NAME AND ADDRESS OF APPLICANT

Healthpoint, Ltd.
307 E. Josephine St.
San Antonio, TX 78215

4. LEGAL BASIS FOR SUBMISSION

See Chemist's Review #1

7. NONPROPRIETARY NAME

Clobetasol Propionate

9. AMENDMENTS AND OTHER DATES:

Original 6/22/92
Amendment 7/16/92
Amendment 11/2/92
Amendment 1/5/93
Amendment 2/26/93
Amendment 4/16/93
Amendment 12/10/93
Amendment 2/8/94
Amendment 4/4/94
Amendment 4/15/96
Amendment 5/30/96
Amendment 12/18/96
Amendment 2/6/97
Amendment 3/27/97
Amendment 4/4/97
Amendment 4/11/97

10. PHARMACOLOGICAL CATEGORY

Anti-inflammatory Corticosteroid

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

(b)4 - Confidential Business

13. DOSAGE FORM

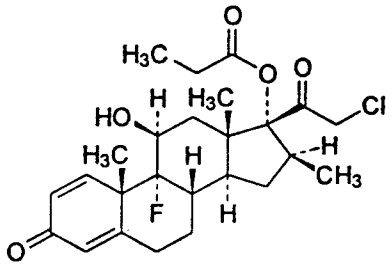
Cream

14. POTENCY

0.05%

15. CHEMICAL NAME AND STRUCTURE

Clobetasol Propionate. $C_{25}H_{32}ClFO_5$. 466.99. Pregna-1,4-diene-3,20-dione, 21-chloro-9-fluoro-11-hydroxy-16-methyl-17-(1-oxopropoxy)-, (11β,16β)-. 25122-46-7. USP 23, page 2626 (Second Supplement).



16. RECORDS AND REPORTS

17. COMMENTS

18. CONCLUSIONS AND RECOMMENDATIONS

The application is approvable.

19. REVIEWER:

/S/

Nashed E. Nashed, Ph.D.

DATE COMPLETED:

4/16/97

4/16/97

Supervisor: Paul Schwartz, Ph.D.

WIV

1. CHEMISTRY REVIEW NO 4

2. ANDA 74-220

3. NAME AND ADDRESS OF APPLICANT

DPT Laboratories, Inc.
307 E.Josephine St.
San Antonio, TX 78215

4. LEGAL BASIS FOR SUBMISSION

See Chemist's Review #1.

5. SUPPLEMENT(s)

N/A

6. PROPRIETARY NAME

N/A

7. NONPROPRIETARY NAME

Clobetasol Propionate

8. SUPPLEMENT(s) PROVIDE(s) FOR:

N/A

9. AMENDMENTS AND OTHER DATES:

Original 6/22/1992
Amendment 2/26/1993
Amendment 4/16/93
Amendment 12/10/93
Amendment 2/8/94
Amendment 4/4/94

10. PHARMACOLOGICAL CATEGORY

Anti-inflammatory

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

(b)4 - Confidential Business

13. DOSAGE FORM

Cream

14. POTENCY

0.5%

15. CHEMICAL NAME AND STRUCTURE

(11B,16B)-21-chloro-9-fluoro-11-hydroxy-16-methyl-17-(1-oxoproxy) pregna-1,4-diene-3,20-dione.

16. RECORDS AND REPORTS

17. COMMENTS

(b)4 - Confidential Business

18. CONCLUSIONS AND RECOMMENDATIONS

The application is not approvable.

19. REVIEWER: DATE COMPLETED:

Nashed E. Nashed, Ph.D. 11/8/94

Supervisor: Paul Schwartz, Ph.D. 11/8/94

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074220

BIOEQUIVALENCE REVIEW(S)

ANDA 74-220

DPT Laboratories, Inc.
Attention: Richard Hammer
100 East 15th Street
Suite 320
Fort Worth TX 76102

OCT 22 1996

Dear Sir:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Clobetasol Propionate Cream 0.05%.

> The Division of Bioequivalence has completed its review and has no further questions at this time.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

/S/

Kaushik Patnaik, Ph.D.
Acting Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

OCT 17 1996

Clobetasol Propionate
Cream 0.05%
ANDA# 74-220
Reviewer: Nhan L. Tran
WP# 742200.496

DPT Laboratories
San Antonio, TX
Submission Dated:
April 15, 1996

Review of a Bioequivalence Amendment

Background:

Clobetasol propionate, an analog of prednisolone, is a synthetic corticosteroid. It is indicated for the short term treatment of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses. The mechanism of anti-inflammatory activity of the topical corticosteroid is unclear.

The extent of percutaneous absorption is determined by many factors including the vehicle. Topical steroids can be absorbed from normal skin. Inflammation and other disease processes in the skin increase percutaneous absorption.

The firm did a double-blind, randomized trial to demonstrate the equivalency of potency of Temovate[R] Cream 0.05% by Glaxo to its product clobetasol propionate cream 0.05%. The Medical Reviewer has reviewed the submission submitted in June 1992, and has found the vasoconstrictor study acceptable from the standpoint of bioequivalence. However, the formulation of the test contains some ingredients which are different from the reference cream, such as Lanolin oil, polysorbate 60, methylparaben and propylparaben. Since Clobetasol propionate is extremely potent in terms of adrenal suppression, the reference and generic cream formulations are sufficient dissimilar to bring into question the safety of the generic product as far as its potential to suppress the HPA axis. The firm therefore was requested to conduct an adrenal suppression study prior to the approval of the cream for bioequivalence. The adrenal suppression was conducted, and submitted, however, the review of the study was not conducted by the Medical Reviewer. The Medical Division (HFD-540) has revised its opinion and has decided that the HPA axis was not necessary (see the Memo from Dr. Wilkin, M.D., Director, HFD 540). Hence, the determination of bioequivalence is based only on the outcome of the vasoconstrictor study.

The formulations are listed below for comparison:

Reference Formulation:

INGREDIENTS	mg/g
Clobetasol propionate	0.05%
Propylene glycol, USP	[redacted]
Glycerine monostearate	
Cetostearyl alcohol	(b)4 -
Glyceryl stearate/PEG 100	nfiden
White wax	
Chlorocresol	usines
Sodium citrate	
Citric acid	[redacted]
Purified water	q.s. 100%

Test Formulation:

Clobetasol propionate	0.0525%
Propylene glycol, USP	[redacted]
Cetyl alcohol	
Stearyl alcohol	
PEG 8 stearate	(b)4 -
White petrolatum	onfidenti
Lanolin oil	Busines
Polysorbate 60	
Glycerol stearate	[redacted]
Methylparaben	
Propylparaben	
Purified water	[redacted]

Comment:

Although Clobetasol propionate is extremely potent in terms of adrenal suppression, since the use of this product is limited to two weeks, as recommended in the labeling, it was decided that an adrenal suppression study for bioequivalence is not needed (see the memo from Dr. J. Wilkin attached).

Recommendation:

The vasoconstriction bioequivalence study conducted by MB & Associates on its 0.05% clobetasol propionate cream, lot # ECAL-5, comparing it to 0.05% Temovate^{R} cream has been found to be acceptable by the Division of Bioequivalence. The test product clobetasol propionate 0.05% cream is therefore deemed bioequivalent to the reference product 0.05% Temovate^{R} cream manufactured by Glaxo Laboratory.

/S/

Nhan L. Tran
Review Branch II
Division of Bioequivalence

RD INITIALED BY SNerurkar
FT INITIALED BY SNerurkar

/S/ 9/11/1996

/S/

Concu Date: 9/25/96
Keith K. Chan, Ph.D.
Director, Division of Bioequivalence

cc: ANDA #74-220 (original), HFD-650 (Tran, Nerurkar), Drug File, Division File.

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

DRUG NAME:	Clobetasol proprionate	**ANDA #:**	74-220
SPONSOR:	MB & Associates		
DOSAGE FORM:	Cream	**STRENGTH:**	0.05%
TYPE OF STUDY:	Vaso-constrictor study.		
STUDY SITE:			
CLINICAL:	(b)4 - Confidential		
ANALYTICAL:	N/A.		

NOT A FIRST GENERIC

STUDY SUMMARY

This was a double blind, randomized, clinical vasoconstrictor study in 36 subjects (8 males and 28 females). At approximately 2:00 PM, 10 mg of the test and reference materials was applied to skin with a glass rod. The treatments sites were covered with a raised perforated guard secured to the skin with non-occlusive tape. Subjects were instructed to keep the treatment sites dry overnight.

At 6:00 AM in the following morning, the protective guards were removed and the test sites were washed with Dove^{R} bar soap and water. At approximately 8:00 AM, the investigator assessed the degree of skin blanching on a scale of 0 to 3 where 0 = non blanching and 1 = mild, 2 = moderate, and 3 = marked blanching. This assessment was repeated at 10:00 AM, 12:00 noon, 2:00 PM, 4:00 PM and 6:00 PM of the same day and at 8:00 AM the following day. Vasoconstriction was scored by two experienced assessors and a consensus judgement was used.

For each formulation, vasoconstriction scores on each arm were summed to produce a single score at each time point. These scores were used to construct the area under the curve using the trapezoidal rule. Mean AUC scores and the mean scores at each time period were compared using the t-test. The 90% confidence intervals of differences between mean scores were calculated and expressed as a percentage of the highest mean score.

The results of the study were reviewed by David C. Bostwick, Medical Reviewer, HFD-540 and found acceptable.

Since the use of this product is limited to not more than two (2) weeks, it was decided by the HFD -540 Division that the adrenal suppression study is no longer needed for the approval of the application.

PRIMARY REVIEWER:	Nhan L. Tran, Ph.D.	**BRANCH:**	II
INITIAL: /S/	**DATE:** 9/9/96		
TEAM LEADER:	Shrinivas Nerurkar, Ph.D.	**BRANCH:**	II
INITIAL: /S/	**DATE:** 9/11/1996		
DIRECTOR, DIVISION OF BIOEQUIVALENCE:	for Keith K. Chan, Ph.D.		
INITIAL: /S/	**DATE:** 10/17/96		

DBE STUDY APPROVAL FORM

ANDA #:	**74-220**	**FIRM:**	**MB & Asso.**	**FIRST GENERIC:**	**NO**
DRUG:	**Clobetasol**	**DOSAGE FORM:**	**Cream**	**STRENGTH:**	**0.05%**
RLD:	**Temovate®**	**FIRM:**	**Glaxo**	**BIO REVIEWER:**	**N. Tran**

Therapeutic Category: Anti inflammatory/Pruritic Dosage Regimen: Varied
Solubility/Permeability: N/A.

Clinical Procedure Summary:

This was a double blind, randomized, placebo-controlled clinical vasoconstrictor study in 36 subjects. Each subject received approximately 10 mg of the test and reference materials on 2 cm^2 of the fore arm skin and the treatment sites were covered with a raised perforated guard secured to the skin with non-occlusive tape for 16 hours. The guards were removed the test sites washed and readings for vasoconstriction were taken two hours later. The degree of vasoconstriction was read according to the following scale: 0 = no blanching, 1 = mild, 2 = moderate, and 3 = marked blanching.

The 90% confidence intervals of differences between mean scores were calculated and expressed as a percentage of the highest mean score.

The results of the study were reviewed by a Medical Reviewer (David Bostwick, HFD-540) and found acceptable.

Center: [redacted](b)4 - Confidential Business[redacted]

# of Subjects Planned:	36	# of Subjects Required:	36
# dropped out:	0	Reasons:	N/A
# of subject completed:	36	# in data analysis:	36
Subset analysis:	N/A	Randomization:	Yes

Demographic: 8 males, 28 females, age between 22-59 y/o.

Safety summary: No adverse effect was observed.

Waiver Request: None.

Comparison to Past Generic Products: **Parameters are comparable.**

OCT 20 1994

Clobetasol Propionate
Cream 0.05%
ANDA# 74-220
Reviewer: Nhan L. Tran
WP# 74220S.692

MB & Associates
Anaheim, CA
Submission Dated:
June 22, 1992

Review of Bioequivalence

Background:

Clobetasol propionate, an analog of prednisolone, is a synthetic corticosteroid. It is indicated for the short term treatment of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses. The mechanism of anti-inflammatory activity of the topical corticosteroid is unclear.
The extent of percutaneous absorption is determined by many factors including the vehicle. Topical steroids can be absorbed from normal skin. Inflammation and other disease processes in the skin increase percutaneous absorption.
The firm did a double-blind, randomized trial to demonstrate the equivalency of potency of Temovate[R] Cream 0.05% by Glaxo to its product clobetasol propionate cream 0.05%.

Objective:

The aim of this study is to compare the standard vasoconstrictor test procedure between the test product, clobetasol cream 0.05% to that of the reference product Temovate[R] cream 0.05% manufactured by Glaxo Laboratory.

Methods and Results: See attached consultative review done by HFD-540.

Formulation:

INGREDIENTS	REFERENCE mg/g
Clobetasol propionate	0.05%
Propylene glycol, USP	(b)4 - Confidential Business
Glycerine monostearate	
Cetostearyl alcohol	
Glyceryl stearate/PEG 100	
White wax	
Chlorocresol	
Sodium citrate	
Citric acid	
Purified water	

INGREDIENTS	Test mg/g
Clobetasol propionate	0.0525%
Propylene glycol, USP	(b)4 - Confidential Business
Cetyl alcohol	
Stearyl alcohol	
PEG 8 stearate	
White petrolatum	
Lanolin oil	
Polysorbate 60	
Glycerol stearate	
Methylparaben	
Propylparaben	
Purified water	

Statistical Analysis

There was no request for consultative statistical review (HFD-513) by the Medical Reviewer of the application.

Comment:

1. The Medical Reviewer has reviewed the submission and has found the vasoconstrictor study acceptable from the standpoint of bioequivalence.
2. The formulation of the test contains some ingredients which are different from the reference cream, such as Lanolein oil, polysorbate 60, methylparaben and propylparaben. However, all those ingredients are within the acceptable limits according to our "INACTIVE INGREDIENT GUIDE".
3. The ingredients which are present in the test and reference formulations are present in different amounts.

Recommendations:

1. The vasoconstriction bioequivalence study conducted by MB & Associates on its 0.05% clobetasol propionate cream, lot # ECAL-5, comparing it to 0.05% Temovate^{R} cream has been found to be acceptable by the Division of Bioequivalence. The test product clobetasol propionate 0.05% cream is therefore deemed bioequivalent to the reference product 0.05% Temovate^{R} cream manufactured by Glaxo Laboratory.

2. Clobetasol propionate is extremely potent in terms of adrenal suppression. In addition, the reference and generic cream formulations are sufficient dissimilar to bring into question the safety of the generic product as far as its potential to suppress the HPA axis. The firm therefore should conduct an adrenal suppression study prior to approval of the cream for bioequivalence.

3. The firm is requested to submit in-vitro drug release rate results for their cream in accordance with the methods proposed in the Pharmacopeial Forum page 5048, March-April 1993. The firm should be informed that in-vitro drug release study is not a requirement for final approval. However, the Office of Generic Drugs requests that this information be included in the submission for semi-solid dosage forms. OGD intends to evaluate such data for the purpose of possibly establishing a batch to batch control tool or developing a possible in-vivo/in-vitro correlation.

The recommendations should be sent to the firm.

Nhan L. Tran /S/
Review Branch II
Division of Bioequivalence

RD INITIALED BY RMHATRE /S/
FT INITIALED BY RMHATRE
10/14/94

Concur: /S/ Date: 10/20/94
Rabindra N. Patnaik, Ph.D.
Acting Director, Division of Bioequivalence

cc: ANDA #74-220 (original), HFD-600 (Here), HFD-630, HFD-130 (JAllen), HFD-344(CViswanathan), HFD-650 (Tran, Patnaik), Drug File.

ANDA 74-220
74-221
74-222

Date of Review: May 4, 1994

Consultative Review of ANDA 74-220, 74-221, 74-222 (Referred by Office of Generic Drugs, HFD-630)

Sponsor: MB and Associates Joint Venture
Anaheim, CA 92808

Product:

74-220	Clobetasol Propionate Cream, 0.05%
74-221	Clobetasol Propionate Ointment, 0.05%
74-222	Clobetasol Propionate Scalp Application, 0.05%

Purpose of Submission: To establish the equivalency of the MB products to the similar Temovate products marketed by Glaxo.

Date of Submission: All of these applications were submitted June 22, 1992.

Investigator: (b)4 - Confidential Business

Background: The vasoconstrictor assay has been used for some time as the test by which the relative potency of topical corticosteroid formulations is established. Because vasoconstrictor methodology was not standardized, and because questions have been raised about the ability of this methodology to detect differences in the potency of topical steroid products, the Office of Generic Drugs (with consultation from ODE II) has devised new methods to test the bioequivalency of topical steroids.

However, it has been decided that ANDA's which were submitted previous to July, 1992 will be reviewed using the "old" standards for evaluation of topical steroid bioequivalency (a single-point vasoconstrictor assay), since the "new" methods standard (a multiple-point vasoconstrictor assay with both mechanical and human measurement of blanching) was not available until recently.

Formulations: The MB and Glaxo cream formulations contain some different ingredients, and the ingredients which are present in both formulations are present in different amounts. The MB and Glaxo ointment and scalp application formulations contain the same ingredients in similar amounts. These facts are important because clobetasol propionate is extremely potent in terms of adrenal suppression, and differences in excipients have been demonstrated to cause different amounts of absorption from the same topical steroid molecule.

Therefore, it is recommended that an adrenal suppression study be performed to support the bioequivalence of the MB cream and Temovate Cream formulations. A policy has been established which requires such a study for clobetasol propionate formulations which do not closely mimic the formulation of the originator product.

Indications: These products are intended for the short-term treatment of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses. The total dosage should not exceed 50 g/week, and the drug should not be used for longer than two consecutive weeks.

Method: Thirty-six healthy males (8) and non-pregnant females (28) were entered into the study. The patients were aged 22-59 years. Four formulations were tested on the volar aspect of each forearm; the generic Cream, Ointment or Scalp Application, the similar Temovate formulation; the vehicle for the relevant generic product, and Diprosone (betamethasone dipropionate) Cream, Ointment or Lotion. Thus, each patient (for example) received the MB Clobetasol Propionate Cream, Temovate Cream, Diprosone Cream and the generic cream vehicle once on each forearm (total of 8 test sites).

The subjects each received approximately 10 mg of each test material on 2 cm^2 test sites in a double-blind,. randomized fashion. The test sites were protected by a raised, non-occlusive plastic guard for 16 hours. The guards were removed., the test sites washed, and readings for vasoconstriction taken two hours later. The degree of vasoconstriction was read according to the following scale:

0 = no blanching
1 = mild blanching
2 = moderate blanching
3 = marked blanching.

A. NDA 74-220 - Clobetasol Propionate Cream, 0.05%

There are twice as many scores as test subjects because the drugs were tested on both forearms.

Number of Patients per Blanching Score

Test Product	0	1	2	3	Mean
Generic Vehicle	67	5	0	0	0.07
MB Clobetasol Propionate	0	6	25	41	2.49
Temovate Cream	1	6	19	46	2.53
Diprosone Cream	3	29	27	13	1.69

B. NDA 74-221, Clobetasol Propionate Ointment

Number of Patients per Blanching Score

Test Product	0	1	2	3	Mean
Generic Vehicle	69	3	0	0	0.04
MB Clobetasol Propionate	0	7	25	40	2.46
Temovate Ointment	0	6	22	44	2.53
Diprosone Ointment	0	24	30	18	1.92

C. NDA 74-222 - Clobetasol Propionate Scalp Application, 0.05%

Number of Patients per Blanching Score

Test Product	0	1	2	3	Mean
Generic Vehicle	71	1	0	0	0.01
MB Clobetasol Propionate	2	8	22	40	2.38
Temovate Scalp Application	3	11	18	40	2.32
Diprosone Lotion	4	19	25	24	1.96

Conclusions: These studies are acceptable from the standpoint of bioequivalence. The reference and generic clobetasol propionate formulations are quite similar in their vasoconstrictor activity. Both the reference and generic products are also markedly superior to Diprosone products of the same dosage form and to the generic vehicle in vasoconstrictor activity.

However, the reference and generic cream formulations are sufficiently dissimilar to bring into question the safety of the generic product insofar as its potential to suppress the HPA axis. Therefore, an adrenal suppression study is necessary prior to approval of the cream for bioequivalence.

[redacted]/S/

David C. Bostwick

[redacted]/S/

Seymour Rand, M.D.

cc: Orig NDA 74-220
74-221
74-222
HFD-630
HFD-520/Bostwick
HFD-540/Rand [redacted]/S/ 8/8/94
HFD-540/Consult File
Y:\bostwick\74-220

[redacted]/S/ 8/9/94

STATISTICAL REPORT

EVALUATION OF THE VASOCONSTRICTIVE EFFECTS OF TOPICAL FORMULATIONS OF CLOBETASOL PROPIONATE AND BETAMETHASONE PROPIONATE CREAMS

Protocol MB #1

Author:

Investigator:

(b)4 - Confidential Business

Sponsor:

MB and Associates Joint Venture
8265 East Somerset Lane
Anaheim, California 92808

INTRODUCTION AND STUDY OBJECTIVE

Vasoconstriction induced by topical corticosteroid application is a commonly used bioassay for the potency of those corticosteroids (1, 2, 3, 4, 5). In this study, the vasoconstriction bioassay was used to compare a generic formulation of clobetasol propionate with an approved brand name product (Temovate®). A less effective corticosteroid preparation (Diprosone® brand of betamethasone dipropionate) and a placebo were also tested.

METHODS

SUBJECT POPULATION

Healthy male or nonpregnant female volunteer subjects, 18 to 60 years of age were eligible to enter the study. Subjects were excluded if they had an active dermatitis or a history of adverse reactions to topical or systemic corticosteroids. Subjects using topical or systemic corticosteroids within one month of the start of the study were also excluded. Informed consent was required and any potential subject judged to be unable to give informed consent was excluded.

TEST DRUGS

The four formulations used were:

Clobetasol Propionate 0.05% cream
Temovate® (brand of clobetasol propionate) 0.05% cream
Diprosone® (brand of betamethasone dipropionate) 0.05% cream
Placebo cream

The test drugs were coded and labeled A, D, F and G. The code has not been revealed to the author of this report.

PROCEDURE

For each subject, the four coded formulations were randomly assigned to four discrete $2cm^2$ sites on the volar aspect of each forearm. At approximately 2:00 PM, 10 mg of each test material was applied to its designated skin site with a glass rod. The treatment sites were, then, covered with a raised perforated guard secured to the skin with non-occlusive tape. Subjects were instructed to keep the treatment sites dry overnight.

At 6:00 AM the following morning, the protective guards were removed and the test sites were washed with Dove® bar soap and water. At approximately 8:00 AM, the

investigator assessed the degree of skin blanching on a scale of 0 to 3 where 0 = no blanching, 1 = mild blanching, 2 = moderate blanching and 3 = marked blanching. This assessment was repeated at 10:00 AM, 12:00 PM, 2:00 PM, 4:00 PM and 6:00 PM of the same day and at 8:00 AM the following day. Vasoconstriction was scored by two experienced assessors and a consensus judgement was used. The assessors had not applied the test materials and did not know the randomization code.

STATISTICAL METHODS

For each formulation, vasoconstriction scores on each arm were summed to produce a single score at each time period. These scores were used to construct two measures of area under the curve (AUC) using the trapezoidal rule. A 10-hour AUC measure was based on scores from 8:00 AM to 6:00 PM on the first day and a 24-hour AUC measure was based on all scores. It should be noted that the 24-hour measure may be less accurate because of the long time period between the last and the next-to-last assessment. Mean AUC scores and the mean scores at each time period were compared using the within-subjects t test. Two-sided p values are reported.

The 90% confidence intervals of differences between mean scores were calculated and expressed as a percentage of the highest mean score.

RESULTS

SUBJECTS

A total of 36 subjects (8 males and 28 females) were entered into the study. Their ages ranged from 22 to 59 years. No score was obtained from subject #32 for Formulation G on the left arm at 12:00 PM. AUC scores were not calculated for this subject.

VASOCONSTRICTIVE EFFECT

Figure 1 shows mean vasoconstriction scores for each of the four formulations. It is apparent that Formulation A is the placebo and that Formulation G is the less effective corticosteroid product (Diprosone®). At all time intervals, Formulation A was significantly worse than all other formulations and Formulation G was significantly worse than Formulations D or F ($p < 0.0003$).

Mean vasoconstriction scores at all time intervals as well as the AUC scores are shown in Table 1. Table 1 also shows statistical comparisons of Formulation D and Formulation F (which appear to be the two formulations of clobetasol propionate). Formulation D showed significantly more vasoconstriction than Formulation F at 4:00

PM ($p = 0.036$), but this appears to be an isolated effect of the sort that may be expected when multiple t tests are performed. The most reliable overall estimate of vasoconstrictive effect, the 10-hour AUC, showed no significant difference between Formulation D and Formulation F ($p = 0.18$).

Confidence intervals based on the 10-hour AUC indicate that there is a 90% probability that the magnitude of vasoconstriction produced by Formulation F ranges from 10.8 percent less to 1.0 percent more than that produced by Formulation D.

Data from individual subjects are shown in Listings 1-4.

CONCLUSION

Formulations D and F are not significantly different. Based on the 90% confidence interval of the 10-hour AUC, Formulation F is estimated to have between 89.2 percent and 101.0 percent of the activity of Formulation D.

REFERENCES

1. Stoughton RB. Arch Derm 1969; 99:753-756.
2. Stoughton RB. Arch Derm 1972; 106:825-827.
3. Maibach HI, Stoughton RB. Med Clinic N Amer 1973; 57:1253-1264.
4. du Vivier A, Stoughton RB. Arch Derm 1975; 111:581-583.
5. Stoughton RB. Dermatologic 1976; 152(Suppl 1):27-36.

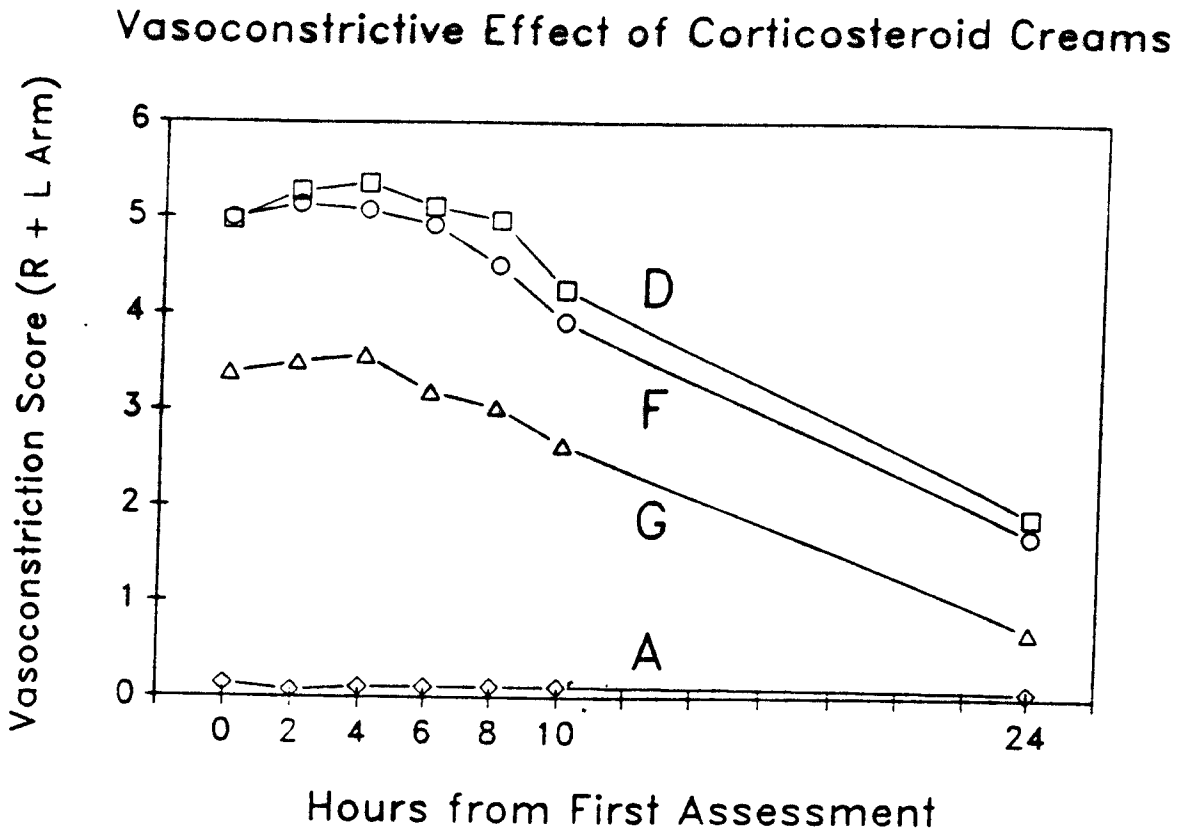


Figure 1. Vasoconstrictive Effects of Corticosteroid Creams over a 24 hour period. Vasoconstriction was scored on a scale of 0 to 3 in each arm and the results from the two arms were summed.

MB and Associates
Vasoconstrictive Effects of Corticosteriod Creams
Protocol MB#1

TABLE 1: Mean Blanching Scores at each Assessment Time and Areas Under the Curve

	D		F		G		A		D minus F			D vs F		90% CI	
Assessment	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	SEM	t	p	Low	High
8:00 AM	36	4.97 (0.91)	36	5.00 (1.10)	36	3.39 (1.20)	36	0.14 (0.42)	36	-0.03 (1.30)	0.22	-0.13	0.899	-6.6	7.7
10:00 AM	36	5.28 (0.78)	36	5.14 (0.93)	36	3.50 (1.00)	36	0.08 (0.28)	36	0.14 (1.38)	0.23	0.61	0.549	-4.5	9.8
12:00 AM	36	5.36 (0.68)	36	5.08 (0.94)	35	3.57 (1.14)	36	0.11 (0.32)	36	0.28 (1.19)	0.20	1.41	0.169	-0.9	11.2
2:00 PM	36	5.11 (0.71)	36	4.92 (1.05)	36	3.19 (0.98)	36	0.11 (0.32)	36	0.19 (1.35)	0.22	0.87	0.393	-3.4	11.0
4:00 PM	36	4.97 (0.94)	36	4.50 (1.21)	36	3.03 (1.18)	36	0.11 (0.32)	36	0.47 (1.30)	0.22	2.18	0.036	2.3	16.7
6:00 PM	36	4.25 (0.97)	36	3.92 (1.25)	36	2.64 (1.07)	36	0.11 (0.32)	36	0.33 (1.10)	0.18	1.83	0.077	0.8	14.9
8:00 AM	36	1.89 (1.21)	36	1.69 (1.37)	36	0.69 (0.89)	36	0.06 (0.23)	36	0.19 (0.95)	0.16	1.23	0.228	-3.5	24.1
AUC 10 hours	36	50.67 (5.93)	36	48.19 (9.03)	35	32.77 (9.25)	36	1.08 (2.93)	36	2.47(10.94)	1.82	1.36	0.184	-1.0	10.8
AUC 24 hours	36	93.64(17.58)	36	87.47(24.30)	35	56.17(19.00)	36	2.25 (6.31)	36	6.17(21.71)	3.62	1.70	0.097	0.2	12.9

All other comparisons were significant: t >= 3.99, p <= 0.0003

AUC: Area Under the Curve, SD: Standard Deviation, SEM: Standard Error of the Mean Difference, CI: Confidence Interval (percent of mean)

Blanching: 0=None, 1=Slight, 2=Moderate, 3=Marked; Because 2 arms are combined, the maximum for each time period is 6